## Remarks/Arguments

**Status of Claims**

Claims 2-6, 8 and 9 are pending in the application and are under substantive examination. Claims 3, 8 and 9 are rejected. Claims 4-6 are objected to. Claim 2 has been determined to recite allowable subject matter.

The claims recite a genus of isolated nucleic acids which are at least 96% identical to SEQ ID NO:1 and which encodes a protein having ORL1 activity. The claims also recite a variant of SEQ ID NO:2 as well as methods of screening compounds for ORL1 activity.

**Claim Amendment(s)**

Claims 3-5, 8 and 9 have been amended. Support for the claim amendments can be found generally in the specification and in the claims as filed.

No new matter has been added by way of the above-described claim amendments

**Specification**

Paragraph [0021] of the specification as filed (which corresponds to paragraph [0032] of publication US2007/027539 has been amended to include sequence identifiers (e.g., SEQ ID NO:2 and SEQ ID NO:3). This amendment brings the specification into compliance with the provision of the sequence listing rules which require disclosed sequences to be assigned a unique sequence identifier which occurs either in the drawing or in the Brief Description.

Paragraph [0064] of the specification as filed (which corresponds to paragraph [0085] of publication US2007/027539 has been amended to correct the SEQ ID NOS: assigned to the primers disclosed in the amended paragraph. More specifically, an incorrect reference to SEQ ID NO:3 has been changed to SEQ ID NO:4, and an incorrect reference to SEQ ID NO:4 has been changed to SEQ ID NO:5. Support for these changes can be found in the original sequence listing filed with the US national stage application which includes all five sequences and their correct designation.

**Information Disclosure Statement**

Applicants note on the record that the information disclosure statement formatting errors noted by the Examiner in the Office Action, will be corrected in the context of a Supplemental

Information Disclosure Statement which will be submitted under separate cover for the Examiner's review and consideration.

**The Objections to Claims 4, 5, 6 and 9 Should be Withdrawn**

Claim 5 is objected to under 37 CFR 1.75 c) as being of improper dependent form for allegedly failing to further limit the subject matter of a previous claim.

Claims 4-6 are objected to because they each depend from claim 1, which is a canceled claim.

Claim 9 is objected to for an alleged lack of clarity.

The above-noted objections have been obviated by:

1) amending Claim 5 to depend from Claim 2. Claim 5 previously had an indirect dependency on claim 1, by virtue of its dependency from Claim 4;
2) amending Claim 4 to depend from Claim 2; which also had the effect of eliminating Claim 6's dependency from canceled Claim 1; and
3) amending Claim 9 to recite numbered subparts for elements a), b), and c).

In light of the above-described claim amendments, Applicants respectfully request that the outstanding objections to claims 4-6 and 9 should be reconsidered and withdrawn.

**The Rejection of Claims 3, 8 and 9 Under 35 USC §112 First Paragraph Should be Withdrawn**

The Disposition of the Claims summary provided on page 2 of the Office Action indicates that Claim 2 is allowed. Therefore, Applicants assume that the rejection under 35 USC §112 first paragraph, set forth in section 5A of the Office Action refers to Claims 3 and 8.

Claims 3 and 8 are rejected under 35 USC §112 first paragraph based on the finding that although the specification is "enabling for the protein of SEQ ID NO:2 and the nucleic acid of SEQ ID NO:1" (Office Action, page 3), it allegedly does not reasonably provide enablement for nucleic acids which hybridize to SEQ ID NO:1, or for any isolated protein having ORL1 activity consisting of SEQ ID NO:2 with a substitution, deletion, addition, or insertion. Based on this finding the Examiner concludes that the specification does not enable a skill person to make the invention commensurate in scope with these claims.

The Examiner notes that "Applicants provide no guidance, or working examples, of nucleic acid molecules which hybridize to SEQ ID NO:1, or of proteins with one or more substitutions, deletions, insertions and/or additions to the protein of SEQ ID NO:2" (Office Action, page 3) characterized by the recited "ORL1 activity."

Claims 3, 8 and 9 have been amended.

As amended, Claim 3 reads:

> 3. A simian isolated nucleic acid consisting of the nucleotide sequence listed as SEQ ID NO:1 or a nucleotide sequence at least 96 % identical to SEQ ID NO:1.

Support for the recitation of the 96% identical limitation can be found in paragraph [0043] of the published application US2007/0275379 wherein alternative embodiments of the nucleic acids of the invention are described as including nucleic acids having 96% homology to the nucleotide sequence set forth in SEQ ID NO:1. Paragraph [0043] also states that "the homology between the rhesus monkey ORL1 gene and the human ORL1 gene is approximately 95.9%, with a difference of 44 nucleotides".

The premise of an enablement rejection based on the scope of the hybribization language has been overcome by virtue of this amendment which limits the scope of the nucleic acids encompassed by Claim 3.

As amended, Claim 8 reads:

> 8. An isolated protein comprising the amino acid sequence set forth in SEQ ID NO:2, or a protein comprising the amino acid sequence set forth in SEQ ID NO:2 with a substitution, deletion, addition or insertion of one, or between 2 and 6amino acids, wherein the protein has ORL1 activity.

Support for the recitation of mutant amino acid sequences embodying variants of SEQ ID NO:2 can be found in paragraph [0046] of the published application US2007/0275379. The cited paragraph provides a description of mutant proteins which Applicants consider to be within the scope of the invention. The text provides literal support for the recitation of ORL1 proteins consisting of the amino acid sequence listed as SEQ ID NO:2 with a substitution, deletion, addition or insertion of one, or between 2 and 6 amino acids, and having ORL1 activity. The premise of an enablement rejection based on the scope of Claim8 has been overcome by virtue of this amendment which limits the scope of the proteins encompassed by Claim 8.

The Examiner further notes that "the scope of Claim 9 is excessive with regard to Applicants claiming a method of screening **any and all ORL1 proteins**" (Office Action, page 4). The Examiner states that Applicants have only taught screening the protein of SEQ ID NO:2.

This rejection has been overcome by amending Claim 9 to read:

9. A Compound evaluation method comprising:

a) 1) a step of transferring a simian Opioid receptor-like 1 (ORL1) gene comprising a nucleotide sequence consisting of the nucleotide sequence listed as SEQ ID NO:1, or a nucleotide sequence at least 96 % identical to SEQ ID NO:1, into a cell to prepare a cell expressing the ORL1 gene,

2) a step of contacting a test compound with the cell, and

3) a step of detecting specific binding of the test compound to a protein obtained by expression of the gene; or

b) 1) a step of transferring a simian Opioid receptor-like 1 gene comprising a nucleotide sequence consisting of the nucleotide sequence listed as SEQ ID NO:1, or a nucleotide sequence at least 96 % identical to SEQ ID NO:1, into a cell to prepare a cell expressing the ORL1 gene,

2) a step of contacting a test compound with the cell,

3) a step of assaying the activity of an intracellular signal transducer produced by the contact between the cell and the test compound, and

4) a step of comparing the activity with the activity of the intracellular signal transducer without contact with the test compound; or

c) 1) a step of contacting a test compound with a simian comprising the amino acid sequence listed as SEQ ID NO:2 with a substitution, deletion, addition or insertion of one, or between 2 and 6 amino acids, and having ORL1 activity, and

2) a step of detecting a change in activity of the protein caused by the contact between the protein and the test compound.

The premise of an enablement rejection based on the scope of Claim 9 has been overcome by virtue of this amendment which limits the scope of the screening method recited in the claim to the proteins disclosed and claimed in the instant application.

In light of the above-described claim amendments, Applicants respectfully request that the outstanding rejection of claims 3, 8 and 9 Under 35 USC §112 first paragraph be reconsidered and withdrawn.

**The Rejection of Claims 3, 8 and 9 Under 35 USC §112 First Paragraph Should be Withdrawn**

The Disposition of the Claims summary provided on page 2 of the Office Action indicates that Claim 2 is allowed. Therefore, Applicants assume that the rejection under 35 USC §112 first paragraph, set forth in section 5A of the Office Action refers to Claims 3 and 8.

Claims 3 and 8 are rejected under 35 USC §112 first paragraph as containing subject matter which was not described in the specification in such a way as to reasonable convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. This rejection was largely based on the scope of the originally filed genus claims, and an allegation that one of skill in the art would reasonably have concluded that the disclosure fails to provide a representative number of species to describe the genus.

As noted above Claims 3 and 8 have been amended. More specifically, as amended Claim 3 no longer defines a genus of nucleic acid molecules based on hybridization. As amended, the scope of claim 3 encompasses only sequences that are at least 96 % identical to SEQ ID NO:1. As amended, Claim 8 now recites a smaller genus of proteins having ORL1 activity which includes a protein having the amino acid sequence listed as SEQ ID NO:2 and a genus of proteins comprising mutants of SEQ ID NO:2 with a substitution, deletion, addition or insertion of one, or between 2 and 6 amino acids. As amended the scope of the claims have been limited to subject matter which a skilled artisan would readily recognize as being in Applicant's possession at the time the application was filed.

In light of the above-described claim amendments, Applicants respectfully request that the outstanding rejection of claims 3, 8 and 9 Under 35 USC §112 first paragraph be reconsidered and withdrawn.

**The Rejection of Claims 3, 5, 8 and 9 Under 35 USC §112 Second Paragraph Should be Withdrawn**

Claims 3, 5, 8 and 9 are rejected under 35 USC §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. More specifically, the Office Action indicates that:

A. Claims 3, 5, 8 and 9 recite the acronym "ORL1," and that as such the acronymn should be spelled upon its first use;

B. Claims 3, 8 and 9 are alleged to be indefinite for recitation of the phrase "ORL1 activity;"

C. Claim 8 is noted to be confusing because it recites the transition phrase "consisting of" to describe a genus of ORL1 proteins which includes variant proteins characterized by an amino acid substitution, addition, deletion or insertion relative to the sequence set forth in SEQ ID NO:2.

The indefiniteness rejections summarized above have been overcome by amending Claim 4, to indicate which represents the first use of the acronym ORL1, to spell out the term Opioid receptor-like 1 and to indicate that the acronym represents this term, and by amending the language of Claim 8 to mere clearly define the genus of variant (e.g., mutant) sequences that it encompasses.

More specifically, Claim 8 has been amended to recite a genus of proteins having ORL1 activity comprising a protein which has defined amino acid sequence as set forth in SEQ ID NO:2 and variant proteins. As amended Claim 8 includes a genus of proteins comprising a protein comprising the amino acid sequence listed as SEQ ID NO:2 and proteins comprising mutants of SEQ ID NO:2 with a substitution, deletion, addition or insertion of one, or between 2 and 6 amino acids.

Applicants respectfully disagree with the Examiner's finding that the term "ORL1 activity" is indefinite. Applicants are of the opinion that the a skilled artisan knows the activity of ORL 1 and can easily identify a suitable assay for measuring ORL1 activity.

This opinion is premised on the fact that the human ORL1 receptor has been de-orphanized by the identification of endogenous agonist peptide for ORL1 receptor. Paragraph [0005] of USPTO patent application US2007/0275379 indicates that the endogenous ligand for human ORL1 is nociceptin (also referred to as orphanin FQ). Accordingly, one of the skill in the art will readily appreciate that simian ORL 1 activity can be measured as cAMP decreasing activity in response to nociceptin activation of the receptor, citing *Eur. J. Neuroscience,* Vol. 9, 194 (1997) and *Neuroscience,* Vol. 75, 1 and 333 (1996) (referred to in paragraph [0005] as Non-patent documents 10 and 11).

Alternatively, as shown in the instant applications, ORL1 activity can be determined as nociceptin-stimulated increase in GTPγS binding (see Fig. 4.) Skilled artisans would be aware of this alternative ORL 1 activity measurement based on the teachings disclosed in *Eur. J. Pharmacol.*

336(2/3), 233-242, 1997, which was published before the priority date of this application. (A copy of this publication has been included with the response for the Examiner's convenience (Exhibit A).

Therefore, based on the information provided in the disclosure and the state of the prior art Applicants do not believe that recitation of the term "ORL1 activity" renders the claims indefinite. In light of the above-described claim amendments and remarks Applicants respectfully request that the outstanding rejection of claims 3, 8 and 9 Under 35 USC §112 second paragraph be reconsidered and withdrawn.

**The Rejection of Claims 3, 8 and 9 Under 35 USC §102 Should be Withdrawn**

Claims 3, 8 and 9 are rejected under 35 USC §102(b) as being anticipated by Evans *et al.* (US 6,432,652). Evans et al teach a nucleic acid encoding an opioid receptor which the Examiner describes as 93.5% identical to SEQ ID NO:1 of the instant invention (Sequence Comparison A included in Office Action). The Office Action indicates that the nucleic acid has "96% similarity with SEQ ID NO:1" (Office Action, page 6) and that it would be expected to hybridize to SEQ ID NO:1 even under the most stringent conditions.

Evans teaches a nucleic acid encoding an opioid receptor which is 93.5% identical to SEQ ID NO:1 of this invention. As amended, Claim 3 encompasses nucleic acids comprising a nucleotide sequence that is at least 96% identical to SEQ ID NO:1. Accordingly, the claimed nucleic acid sequences are different from and patentable over Evans *et al*, because the cited references does not teach each and every element of the claimed sequences, and therefore does not deprive the invention of its novelty.

It is further indicated that "[t]he protein of Evans *et al* is 98.8% identical to SEQ ID NO:2 of the instant invention" (Sequence Comparison B included in the Office Action), noting a substitution at position 43.

Applicants respectfully assert that Evans' amino acid sequence is the same as the sequence displayed in Fig 1 and SEQ ID NO:3 of the instant specification. The Examiner alleged that Evans' protein is 98.8% identical to SEQ ID NO:2 of this invention. Sequence Comparison B provided with the Office Action shows 4 mismatched amino acids and 3 conservative substitutions with respect to the amino acid sequence set forth in SEQ ID NO:2 of this invention.

The sequence alignment presented in the Sequence Comparison B clearly shows that Evans' sequence comprises 4 mismatched amino acids and 3 amino conservative amino acid substitution.

Accordingly, the protein of the instant invention (SEQ ID NO:2) differs from the Evans' protein by a total of 7 amino acids, and the cited prior art patent does not deprive the invention of its novelty. Thus, the simian ORL1 proteins recited in Claim 8 are different from and patentable over Evans *et al* because the cited references does not teach each and every element of the claimed sequences.

The Examiner also states that "Evans also teach the screening methods recited in Claim 9" (Office Action, page 6). As amended, the first step of the methods set forth in subsections a) and b) require the step of:

transferring a simian Opioid receptor-like 1 (ORL1) gene comprising a nucleotide sequence consisting of the nucleotide sequence listed as SEQ ID NO:1, or a nucleotide sequence at least 96 % identical to SEQ ID NO:1, into a cell to prepare a cell expressing the ORL1 gene.

Because Evans' et al does not teach a nucleic acid having the nucleotide sequence set forth in SEQ ID NO:1, or a nucleotide sequence at least 96% identical to SEQ ID NO:1 it does not deprive the screening method of its novelty.

In light of the above-described claim amendments and remarks Applicants respectfully request that the outstanding rejection of claims 3, 8 and 9 under 35 USC §102(b) as being anticipated by Evans et al. (US 6,432,652) be reconsidered and withdrawn.

## Summary

For the reasons set forth hereinabove, Applicants respectfully request that the Examiner reconsider and withdraw the various grounds of rejection and objection, and earnestly solicit allowance of the pending claims.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone her at the number provided below.

Respectfully submitted,

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